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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/069,228	04/27/1998	GREGORY D. PLOWMAN	234/118	3164

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	30

DATE MAILED: 06/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/069,228	Applicant(s) Plowman et al
	Examiner Karen Canella	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____ .

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-5, 9, and 23-37* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-5, 9, and 23-37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1. The request filed on October 10, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/069,228 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 2-5, 9, 23-37 are under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. This application contains sequence disclosures on page 93, line 27, page 94, line 3 and page 96, line 3, that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given the response period of this office action within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Applicant is requested to return a copy of the attached Notice to Comply with the reply.

4. Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 4 fails to further limit claim 3. Claim 3 embodies the genus of polynucleotides which encode the polypeptide of SEQ ID NO:2, or the polynucleotides complementary to said

polynucleotide, wherein the polynucleotides are mammalian. Claim 4 specifies that the polynucleotides are human. There would be no difference in the scope of the polynucleotide of claims 3 and 4 because codon usage and methylation patterns within the genus mammalia is the same.

5. Claim 36 is objected to for the misspelling of hemagglutinin.

6. Claims 9, 25, 26, 28, 35 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites "fused to a second polypeptide" without the identification of a first polypeptide.

It is unclear what the recitation of "said polypeptide" is referring to the ALK polypeptide or the second polypeptide in claim 25.

Claim 26 is vague and indefinite in the recitation of "nucleic acid molecule further encodes a GST fusion protein". It is unclear if this nucleic acid encodes a heterologous protein as part of the fusion protein, or if this nucleic acid encodes only the nucleic acid molecules of claim 2, 23 or 24 fused to GST.

The metes and bounds of claim 35 cannot be determined as it is unclear if the limitation of truncation applies to the dominant negative polypeptides as well as the signaling incompetent polypeptides.

The recitation of "so that the nucleotide molecule is manipulable to contain functional alterations of the nucleic acid sequence that afford an opportunity to promote secretion and/or processing of heterologous proteins encoded therefrom" in claim 28 constitutes an intended use does not influence the limitations of the claim. It is unclear if "the secretion and/or processing of heterologous proteins encoded therefrom" are part of the claim limitations. Amendment of the

claim to recite "The isolated, enriched or purified nucleic acid molecule of claim 2, claim 23 or claim 24, wherein said nucleic acid molecule further comprises restriction endonuclease recognition sites at the 5' end and/or the 3' end." would overcome this rejection.

Claim 35 is vague and indefinite in the recitation of "signaling incompetent" and "dominant negative" without recitation of a specific signal or a reference polypeptide so as to assess competence or incompetence of said signal, and to assess negative dominance in relation to a specific polypeptide. Without reference to a specific signal and a specific peptide to which a comparison is to be made, the metes and bounds of signaling incompetence cannot be determined as any given peptide could be incompetent to signal in a biochemical context in which it is not involved, and likewise a peptide must be set forth against which to measure negative dominance of the polypeptide encoded by the claimed nucleic acids.

Claim 36 recites "insertion of a hemophilus influenza hemagglutinin-tag at position 230". It is unclear if applicant intends to insert the tag in between residues 230 and 231, or if applicant intends to append the tag to a polypeptide consisting of residues 1-203 of SEQ ID NO:2.

7. Claims 29 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the vectors of pBR322, pUC118, pUC119, Col E1, pSC101, pACTC184, pVX, pC194, pC221, pT127, p1J101, BPV, vaccinia, 2-micron circle, lambda-gt10, lambda-gt11, pMAM-neo and pRK5, does not reasonably provide enablement for the vectors of fC31, pAdRSVOES or pKRC. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claims 29 and 34 are dependent on the availability of recited vectors or the nucleic acid sequences of said recited vectors for enablement. A search of the prior art indicates that the phage fC31 was used as a cloning vector only once in 1988 (the abstract of Voeikova et al, Biotekhnologiya, 1988, Vol. 4, pp. 176-182). The language of the publication was Russian and it is not clear that this specific phage is presently available as

ATCC does not list fC31 as part of the collection of bacteriophage. A search of the prior art does not identify any phage, plasmid, construct, vector or shuttle vector by the name of pKRC, or any modified adenovirus construct by the name of AdRSVOES. Accordingly, one of skill in the art could not make the claimed vectors as the starting construct are unknown. A deposit of a cell lines comprising pKRC, pAdRSVOES and fC31, or proof that the vectors are commercially available would overcome this rejection.

8. Claims 5, 9, 31, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated vectors and isolated host cells comprising said vectors, does not reasonably provide enablement for vectors and host cells comprised within a transgenic animal or an animal or human being having been treated by gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. .

Claims 5 and 31 are together drawn to a nucleic aid sequence which comprises a nucleotide sequence that encodes a polypeptide comprising the full length amino acid sequence set forth in SEQ ID NO:2 of is completely complementary to said nucleotide sequence, wherein the nucleic acid molecule further comprises a promoter effective to initiate transcription in a host cell, wherein said host cell is a mammalian cell either in vivo or in tissue culture. Claim 9 is drawn to a recombinant cell comprising the nucleic acids of the instant invention. Claim 33 specifies eukaryotic host cells. Claim 34 is drawn to adenovirus constructs comprising nucleic acids of the instant invention. The specification contemplates the use of the instant polynucleotides for the production of transgenic animals (pages 69-71) and in gene therapy (pages 71-76), however, the specification is not enabling for these uses for the following reasons:

(A)As drawn to gene therapy.

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors

comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that as of 1995, (two years after the priority date for the instant application) clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells

transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that in 1995 current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

(B) as drawn to a transgenic animal

The specification states on pages 52-54 that genetically engineered host cells can be used to produce transgenic non-human animals. The specification does not provide guidance in the making of a transgenic animal comprising the instant recombinant polynucleotides or transformed cells. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. The vectors to be used for directing the expression of transgenes in a given tissue or in all tissues must contain the appropriate regulatory regions (Houdebine, Journal of Biotechnology, 1994, Vol. 34, pp. 269-287, see bridging pages 272-273)

and expression is heavily dependent on the site of integration in the host genom, and the site of integration is presently unpredictable (Houdebine, page 277, column 1). Therefore, it is concluded that one of skill in the art would undergo undue experimentation in order to make the instant recombinant polynucleotides and cells within a transgenic animal.

Amendment of the claims to recite both "isolated vector" and "isolated host cell" would overcome this rejection.

9. Claims 2-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid molecule which is recombinantly expressed and isolated from a mammalian cell or an amplified PCR product which is synthesized using a human mRNA template, does not reasonably provide enablement for an endogenous nucleic acid molecule which is directly isolated, enriched or purified from a mammal or a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 3 and 4 are drawn to the nucleic acid molecules of claim 2, wherein said nucleic acid molecules are isolated, enriched or purified from a mammal or a human. The specification teaches on page 89 that the instant polynucleotides were not detectable by northern analysis in multiple human tissue sources and that PCR had to be used to amplify the DNA for detection. It is reasonable to conclude that the claimed polynucleotides are present in vary small quantities in the tissues which gave a positive result by PCR as these tissues failed to give a positive result b y Northern hybridization. Therefore, on of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to isolate and use such a small quantity of nucleic acid.

10. Claims 23-26 , 28 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:2 and SEQ ID NO:2 lacking residues 1-25, does not reasonably provide

enablement for a nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:2 lacking residues 114-193, residues 137-493 and residues 193-483, or residues 1-25 and residues 26-113, or a nucleic acid sequence encoding a polypeptide having only residues 1-25, residues 114-193, residues 137-493 and residues 193-483 or a polynucleotide encoding a truncated and signaling incompetent or dominant negative mutant of ALK-7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches that residues 1-25 represent signal peptide which is cleaved off of the mature peptide to produce ALK-7. When given the broadest reasonable interpretation, claims 23, section c and claim 24, as drawn to a nucleic acid encoding a polypeptide minimally comprising the signal peptide domain, read on any protein comprising the signal sequence without limitation as to structure or function. The specification teaches only the ALK-7 identified by PCR from human tissues, and the recombinantly produced ALK-7DN and ALK-7TA which are based on the truncation of the peptide before the catalytic domain, and the substitution of a single amino aid within the catalytic domain, respectively. The specification asserts that the polynucleotides encoding SEQ ID NO:2 are associated with metastasis and are present in the Calu-6 lung cancer cell line, but are not present in normal lung (page 90). The prior art teaches that the Calu-6 lung cancer cell line is characterized as a cell line having a high level of metastatic and invasive potential (the abstract of Zucker et al, International journal of Cancer, 1992, Vol. 52, pp. 366-371). The scope of the claims must be commensurate with the scope of the enablement set forth, and the specification provides no teachings for the use of a peptide minimally comprising residues 1-25 of SEQ ID NO:2, absent the remainder of SEQ ID NO:2.. it is unclear how to make or use other nucleic acids encoding proteins which only minimally comprise residues 1-25 of SEQ ID NO:2 which would function in the detection of metastatic lung cancer, and the specification provides no alternate uses for such polypeptides.

Further, claim 24 is drawn in part to a nuclei acid minimally comprising the transmembrane region of SEQ ID NO:2, the cytoplasmic domain and the catalytic domain. Claim 23 is drawn in part to a nucleic acid encoding a polypeptide minimally comprising the transmembrane region and the cytoplasmic domain (residues 114-493), the cytoplasmic domain (resides 137-493) and a partial fragment of the catalytic domain (residues 193-498). It is noted that the specification described the catalytic domain as comprising residues 193 to 485. It is reasonable to assume that polypeptides minimally comprising residues 193 to residues 493 will not have catalytic activity as the complete catalytic site is not present. The scope of the claims must be commensurate with the scope of the enablement set forth and the specification has not taught how to use any nucleic acid encoding a peptide which minimally comprises the catalytic domain, the cytoplasmic domain or an incomplete fragment of the catalytic domain for the detection of metastatic lung cancer.

Claims 35-37 are drawn to a nucleic acid comprising a polynucleotide sequence which encodes a polypeptide comprising the full length sequence of SEQ ID NO:2 except that the polypeptide is truncated and signaling incompetent and/or dominant negative. Claim 36 embodies claim 35 wherein the truncated polypeptide is obtained by insertion of a HA tag at position 203 of SEQ ID NO:2. Claim 37 is drawn to a nucleic acid molecule encoding a constitutively active polypeptide comprising a nucleotide sequence that encodes a polypeptide comprising SEQ ID NO:2 except that Asp has been substituted for Thr at position 194 of SEQ ID NO:2. When given the broadest reasonable interpretation, claim 35 reads on a nucleic acid encoding a polypeptide which is truncated at the amino terminus, yielding a peptide which would comprise only the cytoplasmic domain. As the extracellular domain would be necessary for the binding of a ligand in order for signal transduction to occur intra cellularly, it would be reasonable to conclude that the resultant peptide would be signaling incompetent. The scope of the claims must be commensurate with the scope of the enablement set forth and the specification has not taught how to use a ALK-7TD in the detection of metastatic lung cancer or any nucleic acid encoding a

peptide which minimally comprises a truncated polypeptide of SEQ ID NO:2 for the detection of metastatic lung cancer.

Furthermore, because SEQ ID NO:2 is expressed in such low levels in cell lines and tissues tested that Northern analysis failed to detect said polynucleitdes, it is reasonable to assume that the peptides encoded by SEQ ID NO:2 is said cells and tissues would also be at very low levels. Therefore one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use peptides which minimally comprise the extracelluar domain of SEQ ID NO:2. If one were to generate antibodies to said extracellular portion, said antibodies would not be expected to be useful in the detection of metastatic cancer because the levels of proteins expressed by the cells would be very low, and thus the binding of the antibodies to the cells would also be very low..

Therefore with the exception of full length SEQ ID NO:2, SEQ ID NO:2 lacking residues 1-25 and the full length complements thereof, one of skill in the art would be subject to undue experimentation in order to make and use the broadly claimed invention.

11. Claims 9, 23-26, 28 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to written description

The claims are drawn to polynucleotides comprising a large genus encompassing any polynucleotide which minimally comprises a fragment of SEQ ID NO:2. The claims do not provide a limitation regarding the function of the encompassed polypeptides or polynucleotides, therefore functional attributes which could be used to distinguish proteins which were not members of the genus, from proteins belonging in the genus are missing from the claim. Further, the claims do not limit the structures of the proteins encompasses by genus, beyond minimally

comprising the recited fragments. Claim 35 is included with this rejection because given the broadest reasonable interpretation, the claim could read on the truncation of SEQ ID NO:2 down to a single amino acid residue or down to a fragment of the extracellular domain. Given that a single amino acid residue, or the extracellular domain would be signaling incompetent, these species fall within the limitation of the claim. Further, without a reference to a specific signal, and a specific polypeptide to assess the negative dominant against, one of skill in the art is not able to determine the functional characteristic of peptides which belong within this genus. Thus, the genus is varied as it consists of proteins which are minimally related by structure and which are not related by function. The genus includes proteins which are expressed in metastatic lung cancer but does not exclude proteins which are unrelated to metastatic lung cancer. Thus the disclosure of SEQ ID NO:2 fails to anticipate the structure and function of all the proteins within the claimed genus. One of skill in the art would conclude that applicant has failed to disclosed a representative number of species from within the claimed genus, thus applicant was not in possession of the claimed genus.

(B)As drawn to new matter

Claim 23 is drawn in part to a nucleic acid comprising a sequence encoding the amino acid residues 193-483 of SEQ ID NO:2. The specification teaches that residues 193-485 constitute the catalytic domain of SEQ ID NO:2.(page 52, lines 1-2). This does not provide support for the amendment drawn to the nucleic acid encoding residues 193-483 of SEQ ID NO:2. One of skill in the art would reasonably conclude that applicant was not in possession of the invention at the time of filing.

12. All other rejections and objections as set forth or maintained in Paper No. 20 are withdrawn.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

June 12, 2003